JOURNAL OF NEUROTRAUMA 37:1528–1536 (July 1, 2020)

DOI: 10.1089/neu.2019.6765

White Matter Integrity and Its Relationship to Cognitive-Motor Integration in Females with and without Post-Concussion Syndrome

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Abstract

Fifteen percent of individuals who sustain a concussion go on to develop post-concussion syndrome (PCS). These persistent symptoms are believed to be attributed to damage to white matter tracts and impaired neurotransmission. Specifically, declines in white matter integrity after concussion have been found along the long-coursing axons underlying the frontoparietal network. This network is essential for the performance of visuomotor transformation tasks requiring cognitive-motor integration (CMI). We have previously observed deficits in performance on CMI-based tasks in those who have a history of concussion, but were asymptomatic. The aim of this study was to investigate performance on a CMI task, as well as white matter integrity differences along frontoparietal-cerebellar white matter tracts, in those with PCS compared to healthy controls. We hypothesized an association between the behavioral and brain structural measures. Twenty-six female participants (13 with PCS for ≥6 months and 13 healthy controls) completed four computer-based visuomotor CMI tasks. In addition, diffusion tensor images (DTIs) were acquired. No statistically significant differences were found in CMI performance between groups ($p > 0.05$). Further, there were no statistically significant differences between groups on any DTI metrics ($p > 0.05$). However, examination of the data collapsed across participants revealed significant associations between performance on a CMI task and white matter integrity. Further investigation into additional causes of symptoms in those with PCS (including psychological and cervicogenic factors) will strengthen our understanding of this diverse group. Nonetheless, this study demonstrates that white matter integrity is related to levels of performance in tasks that require rule-based movement control.

Keywords: cognitive-motor integration; post-concussion syndrome; white-matter integrity

Introduction

Concussions, a form of mild traumatic brain injury (mTBI),[1–3] affect an estimated 1.6–3.8 million people in the United States annually,[4,5] with approximately 15% developing persistent symptoms and post-concussion syndrome (PCS).[4,6] Currently, there is no clear consensus on the definition of PCS and its differentiation from persistent symptoms; however, all definitions agree on the presence of symptoms after traumatic brain injury (TBI) that persist beyond the typical symptom recovery time of 1–2 weeks.[7–10] Further, Hiploylee and colleagues[9] suggest that if an individual does not clinically recover over the first 3 years, they may never fully recover. This affects a person's ability to return to their daily life and leads to a high healthcare cost burden.[5,11–13] Females have been suggested to be at an increased risk for PCS, although the underlying mechanisms behind this are not yet known.[11,14] Therefore, it is essential that we not only improve our understanding of the underlying neural effects of concussion and PCS, but also incorporate more objective measurements into recovery assessment to allow for earlier detection and thus earlier intervention.

PCS is thought to occur because of a lack of recovery from damage to axons and white matter tracts sustained in the initial injury, leading to impaired neurotransmission and speed of processing.[12,15–17] White matter changes have been most commonly noted along long-coursing and association tracts, including the corticospinal tract (CST),[18–22] inferior longitudinal fasciculus (ILF),[18,23] superior longitudinal fasciculus (SLF),[18,21,23,24] inferior frontal occipital fasciculus (IFOF),[18,20,22,23] and the interhemispheric commissure—the corpus callosum (CC).[18,19,21,25,26] These tracts underlie the many of the networks required for visually guided reaching movements.[27–30]

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Thus, performance on visuomotor transformation tasks may also be affected after damage to these tracts. The magnetic resonance (MR) imaging (MRI) technique, diffusion tensor imaging (DTI), allows us to indirectly measure the integrity of these white matter tracts after injury.[31]

Visually guided reaching movements are often required in our daily lives, including both standard visuomotor and non-standard visuomotor transformation tasks. A standard task, in which we are looking at the target where we are directing our reaching movement, utilizes a default brain network.[32,33] Whereas non-standard movements, in which the gaze and hand are targeting incongruent spatial locations, must be learned or calibrated and therefore require the integration of cognitive rules. As such, non-standard tasks require cognitive-motor integration (CMI).[29,33] Both types of tasks require the frontoparietal-cerebellar network for accurate movements[27,28,30]; however, reaching tasks, which also require the integration of cognition, are more difficult and therefore incorporate a more complex brain network.[29,34–36] Deficits in CMI performance have been observed in those with a concussion history[1,2] and dementia risk,[37] whereas performance on a standard visuomotor task did not significantly differ from healthy controls in these groups.

Previous research from our laboratory has demonstrated that performance declines in CMI tasks in children and young adults with a history of concussion, but who are asymptomatic based on current standards.[1–3] We have also observed a relationship between white matter integrity and CMI in otherwise asymptomatic older adults at risk for dementia.[38] Many of the tracts showing behaviorally related integrity deficits were part of the networks involved in rule-based movement control. Therefore, non-standard reaching tasks may provide a more thorough assessment of these more complex large-scale brain networks in those with brain injury or impairment, including those with concussion.

Given its crucial role in coordination and feedback-based control of ongoing movements, the cerebellum is putatively essential for CMI-based tasks.[35,39,40] It further plays a role in balance, oculomotor, vestibular, and cognitive functions and thus may be responsible for, or at least related to, many of the symptoms experienced by those with PCS.[27,39] Yet, the effects of concussion and PCS on this structure, and its large white matter tracts (the cerebellar peduncles), has received very little attention to date.[41]

The objectives of this study were 3-fold. The first objective was to investigate the behavioral differences in those with PCS compared to healthy controls on tasks which require CMI. Second, we examined the effect of PCS on white matter integrity, specifically along the tracts underlying the frontoparietal network and the cerebellar peduncles. Third, we examined the associations between performance on CMI tasks, subjective symptom reporting, and white matter integrity. We decided to look specifically at females in this study because of the fact that females have been shown to be at an increased risk for PCS,[11,14] as well as the sex-related differences in neural correlates to CMI performance noted previously in our laboratory.[42] We hypothesized that individuals with PCS would have reduced white matter integrity in tracts that included the frontoparietal-cerebellar network involved in rule-based skilled movement control. From this general hypothesis, we predicted that these individuals would display impaired CMI (but unimpaired standard movement control) relative to healthy controls. We further predicted that the number and severity of reported symptoms would be associated with CMI task performance, with both being related to white matter integrity declines.

Methods

Participants

Twenty-six female participants between the ages of 18–60 were included in this study; 13 with PCS (mean = 30.0 ± 10.8 years) and 13 age-matched healthy controls (mean = 30.0 ± 11.2 years). PCS was defined according to Tator and colleagues[10] as three symptoms lasting at least 1 month after concussive brain injury. This study defined concussion according to the 4th International Consensus Conference on Concussion in Sport[43] as a ''complex pathophysiological process affecting the brain, induced my biomechanical forces.'' Specifically, an injury was considered a concussion if there was a known mechanism of injury (either a direct blow or an impulsive force), which resulted in the rapid onset of at least one sign or symptom. A self-reported concussion was determined as a concussive incident in which there was either a diagnosis by a medical physician or in which the date and mechanism of injury were recalled. The mechanism of injury for each concussion was either a sport-related injury or attributed to a general fall or TBI.

All PCS participants had symptoms persisting for ≥6 months at the time of the study (average = 36.0 ± 28.6 months; range, 6–108). Age-matched control participants who self-reported no previous history of concussion were also recruited. None of the participants had a diagnosed neurological disease, had sustained their TBI from a motor vehicle accident, or were deemed unsafe to undergo MRI. All participants were right-handed, with no injury (other than PCS) that would prevent them from participating in physical activity or sport. Upon examination of MR images, no gross morphological abnormalities were observed in any participants who were included in the study. Information about the concussive injury, including the number of previous concussions and length of time since the concussion, was collected through a questionnaire.

This study was approved by the York University Research Ethics Committee, and all participants provided informed written consent.

Procedure

All participants completed the Sport Concussion Assessment Tool, 3rd Edition (SCAT3), a computerized CMI task (BrDI™) involving four visuomotor transformation conditions, and diffusion-weighted imaging.

Sport Concussion Assessment Tool (SCAT3)

Symptoms were measured through the symptom inventory as part of the SCAT3.[43] The symptom inventory consists of 22 commonly reported symptoms, which were self-rated on a 7-point Likert scale from 0 (no issue) to 6 (severe). Both the number of symptoms (maximum [max] 22) as well as a symptom severity score (sum of all reported symptoms, max 132) were reported. The SCAT3 also incorporates both cognitive (the Sideline Assessment of Concussion [SAC]) and motor (balance and coordination) components. The Sideline Assessment of Concussion (max score 30) measures cognitive ability over four subdomains, including orientation (max 5), immediate memory (max 15), delayed recall (max 5), and concentration (max 5). A higher SAC score indicates higher cognitive ability. Balance is measured through the modified Balance Error Scoring System, incorporating three 20-sec tests of different stances on a firm ground. Deviation from the stance is counted as an error, up to a maximum of 10 errors per stance (max 30 total). The final component of the SCAT3, coordination, looks at the ability to perform five finger-to-nose movements accurately within 4 sec and is scored as yes (1/1) or no (0/1). Each of these different components has shown reliability, sensitivity, and specificity.[44]

Visuomotor task (BrDI)

Participants completed four computer-based visuomotor transformation tasks that included one standard and three non-standard (vision and action decoupled) conditions (Fig. 1). Participants sat at a desk so they could comfortably reach a 10.1-inch tablet (ASUS Transformer Book) placed on the desk in front of them. The tablet was connected to a 15-inch external monitor allowing for a screen in both the horizontal and vertical planes. The monitor was placed 70 cm from the tablet to ensure a consistent visual angle. All hand movements were made on the tablet, which was placed at a 15-degree angle tilted upward toward the participant to allow for comfortable movements.

In all conditions, participants were instructed to slide the index finger of their dominant (right) hand along the touch screen tablet in order to displace a cursor from a central target to one of four peripheral targets (up, down, left, or right relative to center) as quickly and as accurately as possible. Participants guided a crosshair cursor, viewed on a black background, to the yellow central (or home) target, which changed to green when entered. After a 4000-ms center hold time, a red peripheral target was presented and the central target disappeared, which served as the ''Go'' signal for the participant to initiate movement. Once the cursor reached and remained in the peripheral target for 500 ms, it disappeared, signaling the end of the trial. The next trial began with the presentation of the central target after an intertrial interval of 2000 ms. Peripheral targets on the tablet were located 55 mm from the center target, with target diameters of 10 mm. In order to ensure smooth movement of the finger during the task, participants wore a capacitive-touch glove on their right hand.

Participants completed four conditions in a randomized block design. In the standard condition, participants both looked at and moved on the tablet, thereby directly interacting with the targets. The three non-standard conditions required the decoupling of the eyes and the hand: 1) plane change (PC), in which participants looked at the vertical screen while moving on the horizontal tablet screen, requiring implicit sensorimotor recalibration; 2) cue reversal (CR), in which the feedback was rotated 180 degrees (i.e., in order to move the cursor left, you must slide your finger right), requiring explicit strategic control and movements of the eyes and hand to be made in opposite directions. Participants both looked at and moved on the horizontally placed tablet; and 3) plane change plus cue reversal (PC+CR), in which both previously mentioned non-standard tasks were combined, thereby requiring two levels of decoupling. Four trials in each of the four directions were completed per condition for a total of 64 trials per participant (4 directions $\times$ 4 trials $\times$ 4 conditions). Eye movements were monitored by the experimenter to ensure that participants were looking at the correct target. Participants were provided a practice of two trials in each of the four directions before each condition to ensure familiarity of the task in order to obtain the greatest ability of each participant (see Fig. 1).

Data processing

Custom-written (C++) acquisition software sampled the finger's X-Y screen position at 50 Hz. Custom analysis software (Matlab; The MathWorks, Inc., Natick, MA) was used to process individual movement paths with a fourth-order (dual pass) low-pass Butterworth filter at 10 Hz. Filtered paths were used to generate a velocity profile of each trial's movement. Movement onsets and ballistic movement offsets (the initial movement preceding path corrections) were scored at 10% peak velocity, whereas total movement offsets (i.e., including path corrections) were scored as the final time point at which movement decreased back down to 10% peak velocity once the finger position was within the peripheral target. These profiles were then verified by visual inspection and manually corrected, if necessary.

Trials were considered errors if the finger/cursor left the center target before the required center hold time (<4000 ms), reaction time was <150 or >8000 ms, or total movement time was >10,000. Trials in which the first ballistic movement exited the boundaries of the center target in the wrong direction (>90 degrees from a straight line to the target) were coded as direction reversal errors, excluded from calculations of mean values obtained from correct trials, and analyzed as a separate variable. The number of submovements, or corrective movements, was verified by visual inspection. These were defined as a decelerated movement followed by an accelerated movement throughout the movement trajectory. Both the first author researcher and a blinded researcher manually inspected and counted submovements, and the final measure was determined as the average between the scorers. The scored data were then processed to compute both movement timing and execution outcome measures. Trials in which one of the variables was >2 standard deviations (SDs) from the individual's mean score were excluded from further analysis.

Kinematic variables for movement timing were as follows: 1) reaction time (RT), the time interval (milliseconds) between the central target disappearance and movement onset; 2) total movement time (TMT), the time between movement onset and full movement offset (milliseconds); and 3) peak velocity (PV), the maximum velocity obtained during the movement (mm/sec). Kinematic variables for movement execution were: 1) full path length

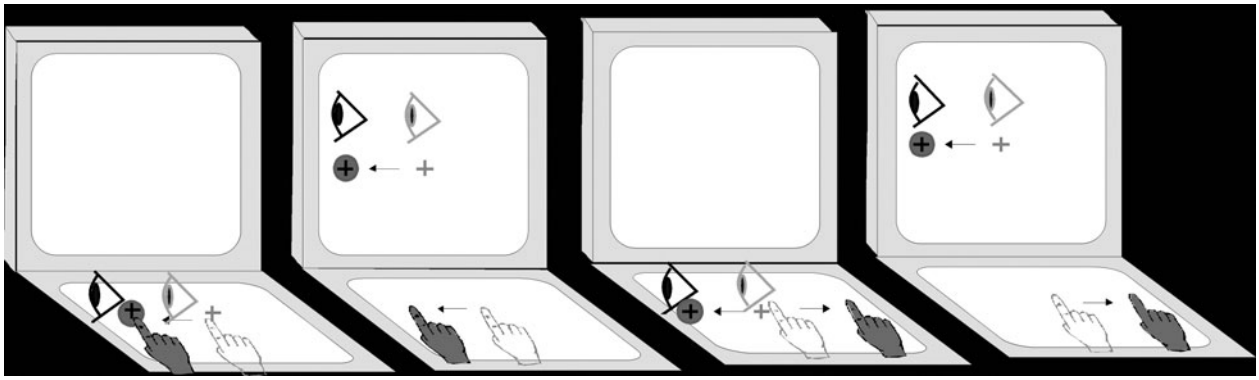

FIG. 1. Schematic drawing of the four experimental conditions. Visual stimuli were presented on either the vertical or horizontal monitor, whereas movement direction was either toward the target or 180 degrees reversed. Light gray cursor, eye, and hand symbols denote the starting position for each trial (home target). Dark gray eye and hand symbols denote the instructed eye and hand movements for each task. Circles denote the peripheral (reach) target, presented randomly in one of four locations (left, up, right, or down). The dark crosshair denotes the cursor feedback provided during each condition.

(FPL), the total distance (resultant of the x- and y-trajectories) traveled between movement onset and offset (millimeters); 2) absolute error (AE; accuracy), the mean distance from the individual ballistic movement endpoints ($\sum$ x/n, $\sum$ y/n) to the actual target location (millimeters); 3) variable error (VE; precision), calculated as the distance between the individual ballistic movement endpoints ($\sigma 2$) from their mean movement (millimeters); 4) the percentage of equal trials (%Equal), determined by the percentage of correct trials in which the initial ballistic movement was equal to that of the full movement, resulting in one smooth movement; 5) percent submovements (%SubMvt), the percentage of correct trials in which submovements were present; 6) number of submovements (#SubMvt), calculated as the mean number of submovements per each correct trial; and 7) direction reversal errors (DR), the percentage of total trials in which a direction reversal error occurred.

Imaging acquisition and parameters

Whole-brain diffusion-weighted images were acquired on a 3-Tesla Siemens Tim Trio scanner at York University using a 32-channel head coil (Siemens, Erlangen, Germany). Diffusion-weighted images were acquired using a single-shot echo planar sequence, including generalized autocalibrating partially parallel acquisition, to increase the signal-to-noise ratio (repetition time = 9200 ms; echo time = 86 ms; slice thickness = 2.0 mm; voxel size = 2.0 mm^3; field of view = 192 mm^2). A total of 64 encoding directions were obtained with b-value = 1000 s/mm^2. In addition, one reference volume with no diffusion weighting was collected (b-value = 0 s/mm^2).

Behavioral data analysis

All data were checked for normal distribution (Shapiro-Wilk's test) and homogeneity of variance (Levene's test). Given that the data violated normality, non-parametric tests were used. This was because of the homogeneity of variance, in that those with PCS demonstrated significantly greater variability compared to healthy controls on a number of behavioral measures. Statistical significance levels were set *a priori* to $p < 0.05$. Statistical analyses were performed using SPSS statistical software (SPSS 24; IBM Corp., Armonk, NY).

To test the main effect of group (PCS, healthy control) on SCAT3 scores, a Mann-Whitney U test was used on each component and corrected for multiple comparisons using Holm-Bonferroni. Likewise, for each of the dependent kinematic variables of the CMI visuomotor task described above (RT, TMT, PV, FPL, AE, VE, %Equal, %SubMvt, #SubMvt, and DR), the Mann-Whitney U test was used to test the main effect of Group (PCS, healthy control) and corrected for multiple comparisons with Holm-Bonferroni.

In order to minimize the number of variables for correlation analyses, composite scores were calculated based on a ''simple averaging'' approach.[45] For each of the included variables, a z-score was calculated (using the control participants' mean and SD) and summed in order to create a timing, trajectory, and submovement composite score for each condition. The timing score included RT, TMT, and the inversed PV (PV z-score * −1). The trajectory score included FPL, AE, and VE, whereas the submovement score included %SubMvt and #SubMvt. Each composite score was then transformed (using a mean of 50, SD 10) for ease of interpretation, with a higher score indicating worse performance. Each transformed score was tested for internal validity using Cronbach's alpha (averaged across conditions). The main effect of group (PCS, healthy control) on the composite scores for each condition was tested using the Mann-Whitney U test.

Imaging analysis

All diffusion-weighted images were analyzed using FMRIB software Library (FSL).[46] First, the effects of head motion and eddy current were corrected using FSL's Diffusion Toolbox (FDT), followed by the removal of non-brain structures using the Brain Extraction Tool (BET).[47] Calculation and fitting of tensor models, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), were completed and extracted using DTIFIT within the FDT. Voxel-wise statistical analysis of the FA data were carried out using Tract-Based Spatial Statistics (TBSS),[48] part of FSL.[49] Specifically, first each FA image was slightly eroded and end slices zeroed in order to remove outliers. All subjects' FA data were then aligned into a common space (FMRIB58), using the nonlinear image registration tool (FNIRT), and registered to the MNI152 space by affine transformation.[50,51] The FMRIB58 template is in the same space as the MNI152 template and is constructed from average FA images of 58 healthy individuals. The MNI152 template is based on 152 T_1-weighted scans transformed (both linearly and non-linearly) to form a symmetric model.

Next, the mean FA image was created and thinned to produce a mean FA skeleton, which represents the centers of all tracts common to the group. Each subject's aligned FA data were then projected onto the mean skeleton. Each subject was manually inspected to ensure that their major white matter tracts lined up with the created mean skeleton. This procedure was then applied to MD, AD, and RD metrics using TBSS for non-FA images. Voxel-wise cross-subject statistics were performed on the resulting data. Specifically, the ''randomise'' algorithm was used, which allows for a non-parametric permutation analysis, to test the main effect of group (PCS, healthy control) in whole-brain FA, MD, AD, and RD values.[52] Multiple comparisons were corrected using a threshold-free cluster enhancement. This technique is more sensitive and robust than both cluster- and voxel-based thresholds, given that one does not arbitrarily pick a threshold, and is thus more effective at preventing increases in false-positive or false-negative results.[53] Because of a relatively small sample size, variance smoothing of 5 mm was used to increase power, and 5000 permutations were run for each metric.

A region of interest (ROI) approach was used to extract FA, MD, AD, and RD measures from white matter tracts chosen *a priori*, including the CC, both the right and left CST, SLF, ILF, IFOF, and both the right and left cerebellar peduncles (superior cerebellar peduncle [SCP]; middle cerebellar peduncle [MCP]; inferior cerebellar peduncle [ICP]). Masks for CST, SLF, ILF, and IFOF were created based on the probabilistic Johns Hopkins University (JHU) White-Matter Tractography Atlas in FSL.[54] The mask of the CC was created based on the Juelich probabilistic atlas,[55] whereas the cerebellar peduncle masks were created based on the cerebellar white matter probabilistic atlas within the spatially unbiased atlas template (SUIT).[56] All atlases used for mask creation are aligned with Montreal Neurological Institute (MNI) space. Each mask was then set at a threshold of 10% and binarized. Mean FA, MD, AD, and RD were then extracted from these regions for each participant using FSL. Each region, including each DTI metric (FA, MD, AD, and RD), was compared between groups (PCS, healthy control), using the non-parametric Mann-Whitney U test in SPSS software (SPSS 24; IBM Corp.), and corrected for multiple comparisons using Holm-Bonferroni.

Correlation analysis

For correlation analysis, group data were combined, and outliers that were >3 SDs from the full sample mean were excluded. Normality (Levene's test) was then rechecked based on the total sample. Because of the violation of normality, the non-parametric Spearman's rho correlation analysis with 1000 sample bootstrapping was used.

A Spearman's correlation analysis was used to determine the association of both the total number of symptoms and symptom severity to each of the composite scores for the four visuomotor

conditions. In addition, the relationship between FA values of each ROI to the behavioral components (the number of symptoms, severity of symptoms, and composite scores of each condition) was analyzed. In order to minimize the number of correlations run, the FA metric was chosen because it is the most commonly investigated measure of diffusion.

Results

Sport Concussion Assessment Tool

The Mann-Whitney U test revealed that the number of symptoms reported by those with PCS (median [Mdn] = 11.0) was significantly higher than that reported by healthy controls (Mdn = 2.0; U = 13.5; $p < 0.001$; $r = 0.72$). Similarly, severity of reported symptoms was significantly higher in those with PCS (median = 21.0) compared to controls (median = 2.0; U = 16.0; $p < 0.001$; $r = 0.64$). No other aspects of the SCAT3 were significantly different between groups after correcting for multiple comparisons ($p > 0.05$).

The most commonly reported symptoms by those with PCS include ''neck pain'' (85%), ''fatigue/low energy'' (85%), and ''headache'' (77%). When looking at symptom severity, those with PCS reported significantly greater severity of ''headache'' (Mdn = 1.0) compared to healthy controls (Mdn = 0.0; U = 27.5; $p = 0.001$; $r = 0.64$). Similarly, those with PCS reported significantly greater severity compared to controls of ''pressure in head'' (Mdn = 1.0 and 0.0 respectively; U = 32.5; $p = 0.001$; $r = 0.64$), ''neck pain'' (Mdn = 2.0 and 0.0; U = 16.0; $p < 0.001$; $r = 0.75$), and ''sensitivity to light'' (Mdn = 2.0 and 0.0; U = 31.5; $p = 0.002$; $r = 0.61$). No other symptoms were significantly different between groups after correcting for multiple comparisons.

Visuomotor task performance (BrDI)

For each of the composite scores, internal validity was tested using Cronbach's alpha. This was then averaged across conditions for an overall measure of validity. The timing composite score consisted of three items (RT, TMT, and inversed PV; $\alpha = 0.79$), the trajectory composite score consisted of three items (AE, VE, and FPL; $\alpha = 0.54$), and the submovement composite score consisted of two items (%Submvt, #Submvt; $\alpha = 0.77$). Group analysis was completed on each variable as well as each composite score for every condition (standard, PC, CR, and PC+CR). For full results, refer to Table 1. There were no significant differences in timing, trajectory, submovement, or error variables between PCS and healthy controls in any condition ($p > 0.05$). However, it is worth noting that there were differences found in group variability across multiple measures. Typically, the PCS group performed worse and had greater variability than the healthy control group, however not statistically significantly so ($p > 0.05$). For example, in each condition, those with PCS had a higher median timing score compared to the median of healthy control participants. However, variability in the PCS group was also much greater.

Table 1. Median Scores between Groups (PCS, Healthy Control) on Kinematic Variables of Each Visuomotor Task Condition

		Condition			
Kinematic variables	*Group*	*Standard*	*Plane change (PC)*	*Cue reversal (CR)*	*Plane-change + cue-reversal (PC+CR)*
Timing composite	Control	44.04	48.78	38.86	47.60
	PCS	66.54	61.65	60.46	65.70
RT (ms)	Control	355.00	351.00	513.00	494.00
	PCS	365.00	385.00	530.00	567.00
TMT (ms)	Control	331.00	538.00	477.00	763.00
	PCS	436.00	608.00	640.00	909.00
PV (mm/s)	Control	130.89	102.19	103.81	73.42
	PCS	104.50	86.74	83.32	63.92
Trajectory composite	Control	48.40	49.69	45.04	44.26
	PCS	52.39	40.99	43.62	33.00
AE (mm)	Control	2.50	3.58	3.25	4.87
	PCS	2.40	3.04	3.27	3.97
VE (mm)	Control	2.32	2.78	3.12	4.37
	PCS	2.42	3.10	2.63	3.74
FPL (mm)	Control	39.40	39.38	39.55	40.61
	PCS	39.92	39.10	39.73	40.82
Submovement composite	Control	49.28	44.34	49.79	53.22
	PCS	67.26	47.36	65.12	46.56
%SubMvt (%)	Control	6.25	50.00	36.84	73.33
	PCS	12.50	53.33	53.33	62.50
#SubMvt (no.)	Control	0.06	0.56	0.41	1.00
	PCS	0.13	0.57	0.57	1.06
%Equal (%)	Control	100.00	71.43	78.95	66.67
	PCS	100.00	78.57	78.57	69.23
DR (%)	Control	0.00	0.00	7.14	8.33
	PCS	0.00	0.00	7.69	5.56

No significant differences between groups were found ($p > 0.05$).

AE, absolute error; DR, direction reversal errors; FPL, full path length; PV, peak velocity; RT, reaction time; TMT, total movement time; VE, variable error; %Equal, percent of trials with no corrective movements; %SubMvt, percent of trials with submovements; #SubMvt, mean number of submovements per trial.

Diffusion tensor imaging

The voxel-wise TBSS analysis demonstrated no significant differences in overall brain FA, MD, AD, or RD between groups (PCS, healthy control). When looking at the specific regions of interest, the Mann-Whitney U test revealed no significant group differences in FA along any white matter tract investigated, including left and right CST, SLF, ILF, IFOF, SCP, MCP, ICP, and the CC ($p > 0.05$). Similarly, no statistically significant group differences were noted in MD, RD, or AD in any of these regions ($p > 0.05$).

Symptoms and regional white matter integrity

The relationship between both the total number of reported symptoms and severity of symptoms and FA of all ROIs was investigated using Spearman's rho correlation. No significant associations were noted between FA of any region and symptom number or severity ($p > 0.05$).

Visuomotor task performance and regional white matter integrity

All correlations were run based on overall composite scores (timing, trajectory, and submovement). Given that no significant group differences were observed for visuomotor task performance or diffusion MRI measures ($p > 0.05$), the data were collapsed across the two groups. Spearman's rho correlation was run on the combined data to explore the relationship between composite scores in each condition and FA for each ROI. No significant associations were found between any of the composite movement scores and FA in any of the ROIs for the standard, PC, or CR conditions ($p > 0.05$).

Notably, however, in the most challenging PC+CR condition, there was a statistically significant association between FA and the trajectory and submovement composite scores. Specifically, a significant relationship was found between the trajectory score and both the right ($r_s = -0.543$; $p = 0.006$, see Fig. 2A) and left ILF ($r_s = -0.481$; $p = 0.017$), as well as both the right ($r_s = -0.475$; $p = 0.019$) and left IFOF ($r_s = -0.419$; $p = 0.041$). In each region, an increase on the rank of trajectory score (and thus worse performance) was associated with a decrease in FA. When looking at the submovement composite score, a significant relationship with FA values was noted in both the right ($r_s = -0.652$; $p = 0.001$; see Fig. 2B) and left ILF ($r_s = -0.585$; $p = 0.003$), both the right ($r_s = -0.547$; $p = 0.006$) and left IFOF ($r_s = -0.596$; $p = 0.002$), left SLF ($r_s = -0.495$; $p = 0.014$), and left CST ($r_s = -0.423$; $p = 0.039$). In all regions, an increase in submovement score (i.e., poorer performance) was associated with a decrease in FA. Finally, we observed no significant associations between FA and the timing composite score ($p > 0.05$). Of note, correlation analysis was also completed on each group separately (PCS, healthy controls) with similar findings.

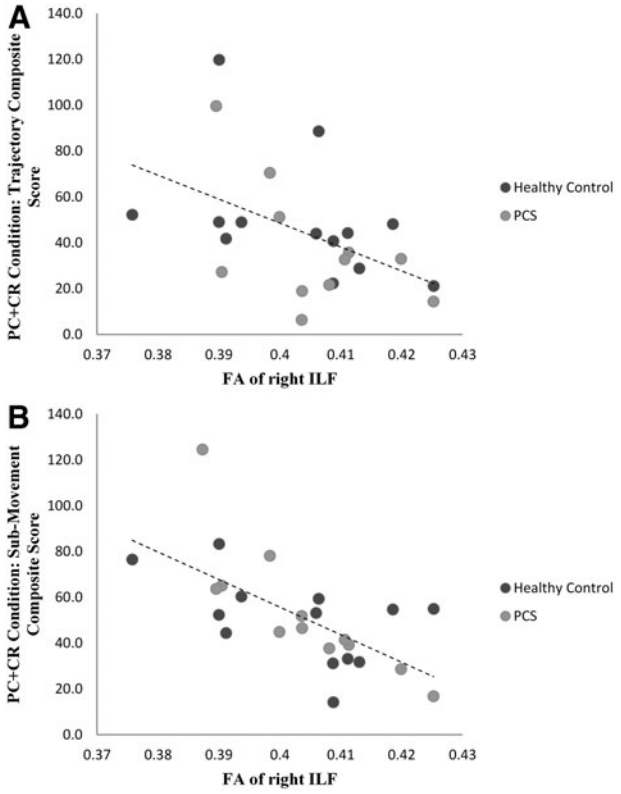

FIG. 2. Graphical representation of the relationship between the FA of the right ILF and performance on the PC+CR task. The composite scores reflect an overall score, with a higher score indicating worse performance. Significant associations were found with the (**A**) trajectory composite score ($r_s = -0.543$; $p = 0.006$) and (**B**) submovement composite score ($r_s = -0.652$; $p = 0.001$). Light circles denote individual participants with PCS, while dark denotes healthy control participants. FA, fractional anisotropy; ILF, inferior longitudinal fasciculus; PC+CR, plane-change with cue reversal; PCS, post-concussion syndrome.

Discussion

The results demonstrated that those with PCS had significantly worse symptom scores relative to healthy controls, but no other significant differences on the remaining aspects of the SCAT3. This finding is not surprising given that presence of self-reported symptoms is required for the diagnosis of PCS, whereas the remainder of the SCAT3 has demonstrated reliability in only acute concussion.[4] Additionally, there were no statistically significant differences between groups on any of the visuomotor transformation task conditions, including both the standard task and those requiring CMI. Similarly, there were no group differences on any DTI metric, at either the whole-brain or ROI level. Importantly, however, when groups were combined, we found a significant association between white matter integrity along the long-coursing association tracts and performance on the most challenging CMI task, requiring two levels of dissociation (PC+CR).

There were no statistically significant differences between those with PCS and healthy controls on any of the visuomotor transformation tasks. Although the median scores found in our study hinted at group differences similar to previous findings in our laboratory,[1–3,37] these non-significant findings may suggest that those with PCS do not demonstrate behavioral differences on rule-based visually guided movements. Recent studies investigating those with persistent symptoms for >3 months have also noted a lack of difference on behavioral tasks when compared to healthy controls.[57,58] Astafiev and colleagues[57] found equivalent performance on a visual tracking task between controls and those with PCS. However, they also noted abnormal activity (blood-oxygen-level–dependent [BOLD] signals) in those with PCS, in that these persons had a different response magnitude resulting in a different shape of the BOLD signal over time. This was found specifically along the SLF. It was suggested that this might reflect a compensatory mechanism, where prolonged

symptoms may result in adequate behavioral performance attributable to altered neural networks.[57] This may explain the adequate behavioral performance in our study; however, further research is required in order to better understand this potential compensatory mechanism.

In addition to a lack of group differences on these visuomotor tasks, there was also a lack of associations with the number or severity of symptoms reported. In fact, as previously mentioned, the only statistically significant finding indicated that a greater number and severity of reported symptoms was associated with improved trajectory performance on the CR condition (in which those with PCS had a better median score). Although the presence of reported symptoms is required for a diagnosis of PCS, this may not be the best indicator of neurological deficits after concussion. The definition of PCS has been controversial,[13,59–62] with many studies finding similar symptom reporting in whiplash disorders,[63,64] chronic pain,[65] depression,[66] and even in seemingly healthy individuals.[67] It may be that our participants had persistent symptoms unrelated to their concussive incident, and thus lacked a relationship between symptoms and neurological deficits. However, to date, it is difficult to determine the etiology of these persistent symptoms; therefore, it is essential to determine more objective measures in order to better understand persistent symptoms and the neurological effects of concussion that may lead to them.

Although the underlying etiology of persistent symptoms after concussion is still unknown, it is believed to be caused by the axonal damage that occurs in the initial injury.[12,16,68] This mechanical shearing of axons leads to altered axonal membrane permeability and cytoskeletal breakdown, which results in slowed conduction and deficits in neurotransmission.[15,17] This has been demonstrated in studies using DTI, in which a reduction in white matter integrity, measured by a decrease in FA, has been found.[21,26,69] Yet, in this study, we found no whole-brain differences on any DTI metric (FA, MD, AD, and RD) between those with PCS and healthy controls. Equally, there were no group differences found on any extracted ROI, including the long-coursing and association tracts we examined (CST, SLF, ILF, IFOF, and CC), and the cerebellar peduncles (SCP, MCP, and ICP). Comparable findings were reported by Maruta and colleagues[58] who also found a lack of significant group differences on any of the global DTI metrics between those suffering from persistent symptoms after concussion and healthy sex- and age-matched controls. When looking at regional differences in FA, they also demonstrated no statistically significant group differences.

The lack of group differences found in our study, as well as in the investigation by Maruta and colleagues,[58] could indicate that those with PCS do not have deficits in white matter integrity, and thus axonal damage is not the underlying etiology of persistent symptoms. Alternatively, these results may indicate that although DTI is currently the best method to detect white matter structural abnormalities,[70] it may not be sensitive enough to the subtle white matter pathologies of persistent symptoms. In addition, it is important to remember that there may be a myriad of reasons for symptoms to persist after concussion, including both psychological and cervicogenic causes. Given that this was not measured in the current study, we are unable to determine whether the symptoms reported were neurological in nature. There may also be a difference, for the particular group that we tested, in ''motor skill reserve'' based on sport experience, which may play a role in mitigating behavioral changes after neural injury.[3]

Although there were no group differences in white matter integrity, we did observe an overall association between FA and visuomotor task performance across all participants. This relationship strengthens the previous findings from our laboratory that performance on our CMI task requires healthy white matter integrity.[34,35,71] Moreover, whereas no significant correlations were found between FA and performance in the standard (default) condition, PC condition (which requires intrinsic sensorimotor recalibration), or CR condition (which requires extrinsic, rule-based strategic control), there were significant associations found in the PC+CR condition (in which both intrinsic and extrinsic recalibration is required). Both the trajectory composite score performance and submovement composite performance were significantly correlated with FA along several long-coursing tracts, including the ILF, IFOF, SLF, and CST. In all cases, a worse performance score was associated with decreased white matter integrity. These results provide further evidence that by decoupling our vision and action in two ways, requiring both implicit and explicit rule integration, there is an increase in task complexity that relies upon large-scale brain network integrity for successful performance.

This study adds to the small body of literature investigating the effects of PCS on both behavior and underlying white matter integrity. To our knowledge, it is the first study to investigate the effects of PCS on cerebellar peduncle integrity and the first study to look specifically at performance on visuomotor tasks requiring CMI in this population. Future research with a larger sample size is required, to account for the fact that there is great heterogeneity in symptom presentation in those with PCS, heterogeneity that may be reflective of underlying differences in neurological impairment. Additionally, investigation into the underlying cause of symptom reporting, including cervicogenic and psychological reasons, is needed in order to better understand the variability observed within this population.

Our observed larger behavioral variability in adults with PCS, relative to healthy individuals, likely reflects the greater biological noise imparted into their movement control systems from their injury. However, the nature of this variability as a function of injury type is an open question. Further investigation on the relationship between mechanism of injury (sport related, falls, or motor vehicle accident) and behavioral variability observed in this population is needed given that this may relate to the differences in the underlying neurological impairment. Moreover, longitudinal studies, in which neurological and behavioral changes can be tracked over time, are required in order to better understand their progression after injury and therefore may help to determine ideal intervention strategies. Last, this study looked specifically at females because of the known neurological differences in both concussion response and skilled movement control between the sexes.[72–76] Consequently, a study investigating males is needed, as well as research into sex, gender, and movement control after brain injury more generally.

In summary, we observed no statistically significant differences between those with PCS and healthy controls on the behavioral measures of CMI, nor on either the whole-brain or ROI measures of white matter integrity. Irrespective, this study highlights the effectiveness of our CMI task in measuring the integrity of long-coursing white matter tracts. We speculate that with a larger sample size, and one that is more uniform in the cause of symptom reporting, we may be able to detect group differences in both white matter integrity as well as task performance. Last, these results demonstrate the need for further studies on this diverse population in hope of better understanding the underlying neurological effects and behavioral changes of persistent symptoms in order to improve the definition and thus diagnosis of PCS.

Funding Information

This research was supported by a Canadian Institutes for Health Research operating grant to LS (MOP-125915) and the Donald Sanderson Memorial Trust Fund (LS, AM, LH).

Author Disclosure Statement

No competing financial interests exist.

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